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(71) Applicant *(for all designated States except US)*: ALCON LABORATORIES, INC. [US/US]; 6201 South Freeway, Fort Worth, TX 76134 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)* : CHOWHAN, Masood [US/US]; 2305 Busch Drive, Arlington, TX 76014 (US).

(74) Agents: CHENG, Julie et al.; Alcon Laboratories, Inc., 6201 South Freeway, Fort Worth, TX 76134 (US).

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(54) Title: USE OF BORATE-POLYOL COMPLEXES IN OPHTHALMIC COMPOSITIONS

(57) Abstract

Water-soluble borate-polyol complexes are useful as buffers and/or antimicrobials in aqueous ophthalmic compositions, including those containing polyvinyl alcohol. These compositions have greater antimicrobial activity than comparable compositions containing typical borate buffers and unexpectedly increase the antimicrobial efficacy of other antimicrobial agents when used in combination. In addition, use of the borate-polyol complexes avoids the incompatibility problem typically associated with the combination of borate buffer and polyvinyl alcohol; therefore, the compositions disclosed herein may also contain polyvinyl alcohol.

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USE OF BORATE-POLYOL COMPLEXES IN OPHTHALMIC COMPOSITIONS

Cross-Reference to Related Applications

This is a continuation-in-part of U.S. Patent Application Serial No. 07/879,435 filed May 6, 1992.

Background of the Invention

This invention relates to the use of borate-polyol complexes in ophthalmic compositions. In particular, these complexes are useful as buffers and/or antimicrobial agents in aqueous ophthalmic compositions, including those ophthalmic compositions containing polyvinyl alcohol.

Ophthalmic compositions are generally formulated to have a pH between about 4.0 and 8.0. To achieve a pH in this range and to maintain the pH for optimal stability during the shelf life of the composition, a buffer is often included. Borate is the buffer of choice for use in ophthalmic compositions, since it has some inherent antimicrobial activity and often enhances the activity of antimicrobials; however, when polyvinyl alcohol (PVA) is also an ingredient in the composition, borate and PVA form a water-insoluble complex which precipitates out of solution and acts as an irritant in the eye. This incompatibility of borate and PVA in contact lens solutions is well-known, and has been discussed, for example, in an article by P. L. Rakow in Contact Lens Forum, (June 1988), pages 41-46. Moreover, borate buffer cannot be effectively used below pH 7.0 due to its low buffering capacity to lower pH.

Since borate is incompatible with PVA, ophthalmic compositions containing PVA are generally buffered with acetate, phosphate or other buffers. There are disadvantages to using these alternative buffers: for example, acetate is a weak

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buffer (pK_a of about 4.5), so a relatively large amount is needed; on the other hand, phosphate is a good buffer but, when used in concentrations generally found in ophthalmic formulations, it reduces the antimicrobial activity of preservatives.

It is well known that small organic compounds, such as benzalkonium chloride (BAC), chlorhexidine, thimerosal have excellent antimicrobial activity; however, it is now known that these small organic antimicrobials are often toxic to the sensitive tissues of the eye and can accumulate in contact lenses, particularly soft, hydrophilic contact lenses. More recently, polymeric antimicrobials such as Polyquad® (polyquaternium-1) and Dymed® (polyhexamethylene biguanide) have been used in contact lens care products as disinfectants and preservatives. While these polymeric antimicrobials exhibit a broad spectrum of antimicrobial activity, they generally have relatively weak antifungal activity, especially against *Aspergillus niger* and *Aspergillus fumigatus*.

A need therefore exists for ophthalmic compositions which have an optimal pH for stability and efficacy, but whose antimicrobial efficacy is not compromised.

Summary of the Invention

This invention provides such ophthalmic compositions. The ophthalmic compositions of the present invention comprise borate-polyol complexes which have surprisingly been found to have increased antimicrobial activity as compared to boric acid or its salts, particularly with respect to organisms such as *A. niger*. Moreover, these complexes unexpectedly increase the antimicrobial efficacy of other antimicrobial agents when used in combination.

The borate-polyol complexes are formed by mixing boric acid and/or its salts with polyols, such as mannitol, glycerin or propylene glycol, in an aqueous solution. The resultant solution may then be used as a buffer and/or antimicrobial agent in

aqueous ophthalmic compositions, even where such compositions also contain PVA. The borate-polyol complexes of the present invention are also useful in unpreserved saline solutions.

The borate-polyol complexes of the present invention are particularly useful as adjunctive disinfecting agents in contact lens disinfecting solutions containing monomeric quaternary ammonium compounds (e.g., benzalkonium chloride) or biguanides (e.g., chlorhexidine) or polymeric antimicrobials, such as polymeric quaternary ammonium compounds (e.g., Polyquad®, Alcon Laboratories, Inc., Fort Worth, Texas) or polymeric biguanides (e.g., Dymed®, Bausch & Lomb, Rochester, New York).

The compositions of the present invention may optionally contain PVA; such compositions are particularly useful in contact lens care products which are targeted for wearers of rigid gas-permeable contact lenses (RGPs), who often complain of discomfort. PVA is a viscosity enhancer and is used extensively in all types of RGP products in order to improve the comfort and wearing time of RGPs. PVA is also extensively used as a viscosity enhancer for pharmaceutical ophthalmic compositions such as eye drops, gels or ocular inserts.

Detailed Description of the Invention

As used herein, the term "borate" shall refer to boric acid, salts of boric acid and other pharmaceutically acceptable borates, or combinations thereof. Most suitable are: boric acid, sodium borate, potassium borate, calcium borate, magnesium borate, manganese borate, and other such borate salts.

As used herein, and unless otherwise indicated, the term "polyol" shall refer to any compound having at least two adjacent -OH groups which are not in *trans* configuration relative to each other. The polyols can be linear or circular, substituted or unsubstituted, or mixtures thereof, so long as the resultant complex

is water-soluble and pharmaceutically acceptable. Such compounds include sugars, sugar alcohols, sugar acids and uronic acids. Preferred polyols are sugars, sugar alcohols and sugar acids, including, but not limited to: mannitol, glycerin, propylene glycol and sorbitol. Especially preferred polyols are mannitol and glycerin; most preferred is mannitol.

The water-soluble borate-polyol complexes of the present invention may be formed by mixing borate with the polyol(s) of choice in an aqueous solution. These complexes can be used in conjunction with other known preservatives and disinfectants to meet preservative efficacy and disinfection standards. In such compositions, the molar ratio of borate to polyol is generally between about 1:1 and about 1:10, and is preferably between about 1:1 and about 1:2.5. The borate-polyol complexes may also be used in unpreserved salines to meet preservative efficacy standards. In these unpreserved salines, the molar ratio of borate to polyol is generally between about 1:0.1 and about 1:1, and is especially between about 1:0.25 and about 1:0.75. Some borate-polyol complexes, such as potassium borotartrate, are commercially available.

The borate-polyol complexes are utilized in the compositions of the present invention in an amount between about 0.5 to about 6.0 percent by weight (wt%), preferably between about 1.0 to about 2.5 wt%. The optimum amount, however, will depend upon the complexity of the product, since potential interactions may occur with the other components of a composition. Such optimum amount can be readily determined by one skilled in the formulatory arts.

The compositions of the present invention useful with RGPs or compositions such as eye drops, gels or ocular inserts will preferably also contain PVA or other viscosity-enhancing polymers, such as cellulosic polymers or carboxy vinyl polymers. PVA is available in a number of grades, each differing in degree of polymerization, percent of hydrolysis, and residual acetate content. Such differences affect the physical and chemical behavior of the different grades. PVA can be divided into two broad categories, i.e., completely hydrolyzed and partially

hydrolyzed. Those containing 4% residual acetate content or less are referred to as completely hydrolyzed. Partially hydrolyzed grades usually contain 20% or more residual acetate. The molecular weight of PVA's vary from 20,000 to 200,000. In general, PVA used in ophthalmic products has an average molecular weight in the range of 30,000 to 100,000 with 11% to 15% residual acetate. Compositions of the present invention generally contain such types of PVA at a concentration less than about 10.0 wt%, preferably between about 0.1 and about 1.4 wt% and most preferably at a concentration of about 0.75 wt%.

EXAMPLE 1

The water-soluble borate-polyol complexes of the present invention may be prepared as illustrated below.

	FORMULATION (% weight/volume)							
INGREDIENT	A	B	C	D	E	F	G	H
Boric acid	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35
Sodium borate	0.11	0.11	0.11	0.11	0.11	0.11	0.11	0.11
Mannitol	0.5	1.0	1.5	2.0	—	—	—	—
Glycerin	—	—	—	—	0.5	1.0	1.5	2.0
Na_2EDTA	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
HCl/NaOH	pH 7.4	pH 7.4	pH 7.4	pH 7.4	pH 7.4	pH 7.4	pH 7.4	pH 7.4
Polyquad®	0.001 + 10% xs	0.001 + 10% xs	0.001 + 10% xs	0.001 + 10% xs	0.001 + 10% xs	0.001 + 10% xs	0.001 + 10% xs	0.001 + 10% xs

Preparation:

Formulations A - H were prepared as follows. Tubular, labeled and calibrated 150 milliliter (mL) beakers were each filled with about 90 mL of purified water. Boric acid, sodium borate and mannitol or glycerin were then added and dissolved by stirring the solution for about 25 minutes. At this time, disodium EDTA (ethylene diamine tetraacetic acid) was added with stirring. Purified water

was added to bring the solutions almost to 100% (100 mL), pH was adjusted to approximately 7.4 and the osmolality was measured. Polyquad® was then added and the volume brought to 100% by the addition of purified water. pH was again measured and adjusted, if necessary, and the osmolality was measured again.

It is not always necessary to have an isotonic solution; however, if there is a need to have an isotonic solution, the osmolality can be adjusted by incorporating polyol with OH groups in *trans* position, sodium chloride, potassium chloride, calcium chloride or other osmolality building agents which are generally acceptable in ophthalmic formulations and known to those skilled in the art.

EXAMPLE 2

Aqueous ophthalmic compositions of the present invention may be prepared using the formulations illustrated below.

	FORMULATION (percent by weight)								
INGREDIENT	1	2	3	4	5	6	7	8	9
PVA	0.75	1.4	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Hydroxyethyl cellulose (HEC)	—	—	0.75	0.28	0.28	0.28	0.28	0.75	0.75
Mannitol	2.0	2.0	2.0	2.0	2.0	2.0	0.5	2.0	2.0
Boric acid	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35
Sodium borate	0.11	0.11	0.11	0.11	0.11	0.11	0.11	0.11	0.11
Edetate disodium	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Sodium chloride	0.09	0.09	0.09	0.09	0.45	0.09	0.09	0.09	0.09
Polyquad®	0.001	0.001	0.001	0.001	0.001	0.001	0.001	—	—
Sucrose	—	—	—	—	—	2.5	—	2.5	2.5
Polyhexamethylene biguanide	—	—	—	—	—	—	—	0.0005	—
BAC	—	—	—	—	—	—	—	—	0.004

Preparation:

Formulations 1 - 9 were prepared as follows. A first solution (Solution A) was prepared by adding 500 mL of warm purified water to a calibrated two liter aspirator bottle equipped with a magnetic stirrer. PVA and hydroxyethyl cellulose were then added to Solution A and the contents dispersed by stirring. After dispersal of the polymers, a filter assembly was attached to the aspirator bottle (142 mm Millipore filter holder with 0.2 μ filter), and this whole apparatus autoclaved at 121°C for 30 minutes. Solution A with the filter assembly attached was then allowed to cool to room temperature with stirring. A second solution (Solution B), was prepared in a 500 mL beaker containing 300 mL of purified water by adding boric acid, sodium borate and mannitol and dissolving the contents by stirring for 25 minutes. Edetate disodium, sodium chloride, preservatives and other osmolality-building agents, as necessary, were added to Solution B and the contents dissolved with stirring. Solution B was then sterile filtered into the aspirator bottle containing Solution A. The pH of the resultant solution was then adjusted and the volume brought to 100% by sterile filtering purified water.

EXAMPLE 3

The following ophthalmic compositions of the present invention may also be prepared using the procedure detailed in Example 2.

	FORMULATION (percent by weight)									
INGREDIENT	10	11	12	13	14	15	16	17	18	19
PVA	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4
Naphazolene HCl	0.1	0.1	—	—	—	—	—	—	—	—
Sodium sulfacetamide	—	—	—	10.0	—	—	—	—	—	—
Fluorometholone	—	—	—	—	0.1	—	—	—	—	—
Gentamycin sulfate	—	—	—	—	—	0.4	—	—	—	—
Levobunolol HCl	—	—	0.5	—	—	—	—	—	—	—
Mydrysone	—	—	—	—	—	—	1.0	—	—	—
Pilocarpine nitrate	—	—	—	—	—	—	—	1.0	1.0	1.0
Sodium metabisulfite	—	—	0.4	—	—	—	—	—	—	—
Mannitol	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	4.0	0.5
Boric acid	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.5
Sodium borate	0.11	0.11	0.11	0.11	0.11	0.11	0.11	0.11	—	—
Sodium chloride	0.45	0.45	0.45	—	0.45	0.45	0.45	0.45	—	—
Edetate disodium	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
BAC	0.004	—	—	—	—	—	—	—	—	—
Polyquad®	—	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001

EXAMPLE 4

The following is a typical wetting and soaking composition of the present invention for use with RGPs.

INGREDIENT	AMOUNT (wt%)
PVA	0.75
HEC	0.38
Boric acid	0.35
Sodium borate	0.11
Mannitol	2.0
Potassium chloride	0.038
Magnesium chloride	0.02
Calcium chloride	0.0154
Sodium chloride	0.09
Polysorbate 80	0.005
Polyquad®	0.001
NaOH and/or HCl	pH 7.4
Purified water	q.s.

Preparation:

In a suitable container containing approximately 30% of the final volume of purified water, PVA and HEC were added and dispersed. This solution was then autoclaved. The solution was allowed to cool to room temperature with stirring. In a separate container, containing approximately 50% of the final volume of purified water, boric acid and sodium borate were added, and dissolved, followed by mannitol. This second solution was then stirred for about 30 minutes, then potassium chloride, calcium chloride, magnesium chloride, sodium chloride, polysorbate 80 and Polyquad® were added, with stirring. The second solution was then added to the first solution via a 0.2 μ filter. Last, the pH was adjusted to 7.4 and the volume brought to 100% with purified water.

EXAMPLE 5

The following is a typical daily cleaner composition of the present invention for use with RGPs and may be prepared in a manner similar to that detailed in Example 4.

INGREDIENT	AMOUNT (wt%)
Nylon 11	2.50
Dextran 70	6.0
Sodium borate	0.25
Boric acid	0.50
Miracare® 2MCA	0.50
PDMA-1	0.15
Propylene glycol	10.0
Polyquad®	0.0055
EDTA	0.10
Mannitol	1.20
NaOH and/or HCl	pH 7.4
Purified water	q.s.

EXAMPLE 6

The following is a typical wetting and soaking composition of the present invention which may be prepared in a manner similar to that detailed in Example 4.

INGREDIENT	AMOUNT (wt%)
Hydroxypropyl methylcellulose (Methocel® E4M)	0.72
Mannitol	1.0
Sodium borate	0.11
Boric acid	0.35
Sodium chloride	0.19
Polyquad®	0.0011
EDTA	0.10
NaOH and/or HCl	pH 7.4
Purified water	q.s.

EXAMPLE 7

The following is a typical comfort drop composition of the present invention which may be prepared in a manner similar to that detailed in Example 4.

INGREDIENT	AMOUNT (w/v%)
PVA	0.75
HEC	0.28
Mannitol	2.0
Sodium borate	0.11
Boric acid	0.35
Sodium chloride	0.152
Polyquad®	0.00082
EDTA	0.10
NaOH and/or HCl	pH 7.4
Purified water	q.s.

EXAMPLE 8

The following is a typical RGP cleaner composition of the present invention which may be prepared in a manner similar to that detailed in Example 4..

INGREDIENT	AMOUNT (wt%)
French Naturelle® ES (Nylon 11)	2.5
Hydroxyethyl cellulose	0.4
Sodium borate, decahydrate	0.25
Boric acid	0.50
Mannitol	3.5
Miracare® 2MCA)	0.50
Isopropyl alcohol (v/v)	10.0
NaOH and/or HCl	q.s. 7.4
Purified water	q.s.

EXAMPLE 9

The following is a typical RGP wetting and/or soaking composition of the present invention., which may be prepared in a manner similar to that detailed in Example 4.

INGREDIENT	AMOUNT (wt%)
Methocel® E4M	0.85
Mannitol	2.00
Sodium borate	0.11
Boric acid	0.35
Sodium chloride	0.19
Disodium edetate	0.1
Polyquad®	0.001
NaOH and/or HCl	pH 7.4
Purified water	q.s.

EXAMPLE 10

The following study compared the antimicrobial preservative efficacy of two wetting, soaking and disinfecting solutions: one containing phosphate buffer (Formulation A); and the other containing a borate-polyol complex of the present invention (Formulation B).

Formulations A and B are shown in the following table.

INGREDIENT	FORMULATION (wt%)	
	A	B
PVA	0.75	0.75
HEC	0.5	0.5
Sodium phosphate	0.67	—
Sodium biophosphate	0.017	—
Boric acid	—	0.35
Sodium borate	—	0.11
Mannitol	—	2.0
Disodium edetate	0.1	0.1
Sodium chloride	0.458	0.153
Polysorbate 80	0.005	0.005
Benzalkonium chloride	0.01	0.01
Purified water	q.s.	q.s.

Formulations A and B were tested against FDA challenge organisms. The log reductions after 1 hour are tabulated below:

TEST ORGANISM	FORMULATION (log reduction)	
	A	B
A. niger	2.1	4.4
B. albicans	4.0	5.3
P. aeruginosa	5.3	5.3
S. aureus	5.5	5.2
E. coli	5.5	5.5

The results shown above indicate that Formulation B (containing borate-polyol complex) has a broader spectrum of activity than Formulation A (containing phosphate buffer), and has greater activity against certain organisms, such as *A. niger*.

EXAMPLE 11

The following study compared the antimicrobial preservative efficacy of two unpreserved saline solutions identical except that one contained a borate-polyol complex of the present invention (Formulation C) and the other contained the conventional borate buffer (Formulation D).

An organism challenge approach based on the British Pharmacopoeia ("BP") 1988 Test for Efficacy of Preservatives in Pharmaceutical Products was used to evaluate the antimicrobial preservative efficacy of Formulations C and D. Formulation samples were inoculated with known levels of *A. niger* and sampled at predetermined intervals to determine if the system was capable of killing or inhibiting the propagation of organisms introduced into the products.

Formulations C and D are shown in the following table.

INGREDIENT	FORMULATION (wt%)	
	C	D
Boric acid	1.0	1.0
Sodium borate	0.2	0.2
Mannitol	1.5	—
Sodium chloride	—	0.3
Disodium edetate	0.1	0.1
NaOH and/or HCl	pH 7.4	pH 7.4
Purified water	q.s.	q.s.

The results indicated that there was a 3.1 log reduction of *A. niger* with Formulation C and only 1.2 log reduction with Formulation D after 7 days. Formulation C met the BP standards for preservative efficacy against *A. niger*, while Formulation D failed to meet the BP standards.

EXAMPLE 12

The following study compared the antimicrobial preservative efficacy of two disinfecting solutions identical except that one contained a borate-polyol complex of the present invention (Formulation E) and the other contained the conventional borate buffer (Formulation F).

An organism challenge approach based on the BP 1988 Test for Efficacy of Preservatives in Pharmaceutical Products was used to evaluate the antimicrobial preservative efficacy of Formulations E and F. Formulation samples were inoculated with known levels of *A. niger* and sampled at predetermined intervals to determine if the system was capable of killing or inhibiting the propagation of organisms introduced into the products.

Formulations E and F are shown in the following table.

INGREDIENT	FORMULATION (wt%)	
	E	F
Boric acid	0.3	0.35
Sodium borate	0.11	0.11
Mannitol	0.85	—
Sodium citrate	0.56	0.56
Citric acid	0.021	0.21
Sodium chloride	0.48	0.48
Pluronic P103	0.5	0.5
Disodium edetate	0.05	0.05
Polyquad®	0.001	0.001
NaOH and/or HCl	pH 7.0	pH 7.0
Purified water	q.s.	q.s.

The results indicate that there was a 2.1 log reduction of *A. niger* with Formulation E and only 1.1 log reduction with Formulation F after 7 days. Formulation E met the BP standards for preservative efficacy against *A. niger*, while Formulation F failed to meet the BP standards.

The invention has been described by reference to certain preferred embodiments; however, it should be understood that it may be embodied in other specific forms or variations thereof without departing from its spirit or essential characteristics. The embodiments described above are therefore considered to be illustrative in all respects and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description.

What is Claimed is:

1. An aqueous ophthalmic composition comprising between about 0.5 and about 6.0 wt% of a water-soluble borate-polyol complex.

2. The aqueous composition of claim 1, wherein the water-soluble borate-polyol complex is present at a concentration between about 1.0 and 2.5 wt%.

3. The aqueous composition of claim 1, wherein the water-soluble borate-polyol complex comprises borate and polyol in a molar ratio between about 1:0.1 and about 1:10.

4. The aqueous composition of claim 3, wherein the water-soluble borate-polyol complex comprises borate and polyol in a molar ratio between about 1:0.25 and about 1:2.5.

5. The aqueous composition of claim 1, wherein the water-soluble borate-polyol complex comprises a polyol selected from the group consisting of sugars, sugar alcohols and sugar acids.

6. The aqueous composition of claim 2, wherein the polyol is selected from the group consisting of mannitol, glycerin, propylene glycol and sorbitol.

7. The aqueous composition of claim 6, wherein the polyol is selected from the group consisting of mannitol and glycerin.

8. The aqueous composition of claim 7, wherein the polyol is mannitol.

9. The aqueous composition of claim 1, further comprising less than or equal to about 10 wt% of a viscosity-enhancing polymer selected from the group consisting of: polyvinyl alcohol, cellulosic polymers, and carboxy vinyl polymers.

10. The aqueous composition of claim 9, wherein the viscosity-enhancing polymer comprises polyvinyl alcohol.

11. The aqueous composition of claim 9, wherein the polyvinyl alcohol is present at a concentration between about 0.1 and about 1.4 wt%.

12. The aqueous composition of claim 1, further comprising an ophthalmically acceptable antimicrobial agent.

13. The aqueous composition of claim 1, wherein the ophthalmically acceptable antimicrobial agent is selected from the group consisting of: monomeric and polymeric quaternary ammonium compounds and their ophthalmically acceptable salts, monomeric and polymeric biguanides and their ophthalmically acceptable salts, and combinations thereof.

14. A method of preparing an aqueous ophthalmic composition, comprising the steps of preparing a water-soluble borate-polyol complex by mixing borate and a polyol together in an aqueous solvent and adding polyvinyl alcohol thereto.

15. The method of claim 14, wherein the water-soluble borate-polyol complex comprises borate and polyol in a molar ratio between about 1:0.1 and about 1:10.

16. The method of claim 15, wherein the water-soluble borate-polyol complex comprises borate and polyol in a molar ratio between about 1:0.25 and about 1:2.5.

17. The method of claim 14, wherein the concentration of the water-soluble borate-polyol complex in the final composition is between about 0.5 and about 3.0 wt%.

18. The method of claim 17, wherein the concentration of the water-soluble borate-polyol complex in the final composition is between about 1.0 and about 2.0 wt%.

19. The method of claim 14, wherein the water-soluble borate-polyol complex comprises a polyol selected from the group consisting of sugars, sugar alcohols and sugar acids.

20. The method of claim 19, wherein the polyol is selected from the group consisting of mannitol, glycerin, propylene glycol and sorbitol.

21. The method of claim 20, wherein the polyol is selected from the group consisting of mannitol and glycerin.

22. The method of claim 21, wherein the polyol is mannitol.

23. Use of a water-soluble borate-polyol complex as a buffering agent for aqueous ophthalmic compositions.

24. Use of a water-soluble borate-polyol complex as an ophthalmic antimicrobial agent.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 93/04226

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K9/00

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	EP,A,0 109 561 (USV) 30 May 1984 see claims 1-2,4-7,9-12 see page 6, line 30 - line 37 see examples D,G,H ---	1,6, 9-10,12, 14,23-24
X	FR,A,2 230 358 (FISONS) 20 December 1974 see claims 9-11 see page 3, line 19 - line 25 see examples ---	1,6, 9-10,12, 14,23-24
X	EP,A,0 436 726 (EISAI) 17 July 1991 see claims 1-2,5 see page 6, line 35 - line 50 -----	1,6, 9-10,12, 14,23-24

° Special categories of cited documents :[10]

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"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
11 AUGUST 1993	18. 08. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	SCARPONI U.

Form PCT/ISA/210 (second sheet) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

US 9304226
SA 73857

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
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